Original Article

Predictive Capability of Blood Test Results on Postoperative Day 3 for Short-term Outcome and Morbidities

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Key Words
Postoperative day 3 CRP;
Colorectal surgery;
Anastomotic leakage

Background. Anastomotic leakage is a notable postoperative complication in patients who undergo elective colorectal cancer surgery. This study aimed to improve the early identification and intervention of serious postoperative complications by comparing preoperative and third-day postoperative blood markers, as well as examining other potential complications.
Material and Methods. A total of 1,298 patients who underwent elective colorectal surgery between 2018 and 2020 were included in this study. Each patient underwent comprehensive blood biochemical examinations both preoperatively and on the third postoperative day. Patients were categorized into groups based on the presence or absence of complications during their hospital stay. Multivariate and regression analyses were conducted using the biochemical markers obtained on the third postoperative day to identify significant predictors of postoperative complications.
Result. Of the 1,298 assessed patients, 730 were included in the final statistical analysis. The patient population at a higher risk of complications consisted predominantly of elderly individuals and those who underwent low anterior resection surgeries. Multivariate analysis identified statistically significant predictive markers for complications, notably lymphocytes ($p = 0.008$) and C-reactive protein (CRP) ($p < 0.001$). Regression analysis further revealed that CRP was a substantial predictor for complications classified as Clavien-Dindo Score ≥ 3, achieving an area under the curve of 0.72. The optimal cutoff value for CRP was determined to be 118.98.
Conclusion. Measurement of CRP levels in blood samples drawn on the third postoperative day serves as a reliable predictive indicator of the potential development of severe complications in patients. This finding enables early clinical intervention aimed at mitigating the adverse outcomes associated with postoperative complications.

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Despite the progress in surgical procedures and the development of stapling tools, anastomotic leakage remains a particularly critical and detrimental issue in colorectal surgery.[1,2]

Predicting severe complications and overall recovery after elective colorectal surgery to guarantee safe and prompt discharge of patients poses a significant challenge when using biological markers.[3] Nu-

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merous research and comprehensive meta-analyses have indicated that the biomarker C-reactive protein (CRP) can effectively predict complications following elective colorectal surgery, such as anastomosis leakage.[4] Notably, CRP demonstrated a robust ability to rule out infective complications and anastomotic leakage with high negative predictive values of 89% and 97%, respectively.[5] Historically, multiple investigations have endeavored to delineate the threshold levels of inflammatory biomarkers, below which the likelihood of postoperative infections is considerably reduced. The most pertinent biomarkers identified in this context were CRP and procalcitonin (PCT).[6,7] Given the cost considerations associated with procalcitonin in the healthcare system of Taiwan, the focus of this study was directed towards the practicality and effectiveness of employing CRP as a single measurement to predict postoperative complications. By evaluating various blood parameters on postoperative day 3, the study aimed to determine their predictive capability for short-term outcomes within a 30-day period.

This research not only contributes to the existing body of knowledge but also holds implications for enhancing clinical decision-making and patient care in the field of colorectal surgery.

Patients and Methods

A single medical center conducted a retrospective chart review of adult patients who underwent colorectal cancer surgeries between 2018 and 2020. Patients were included if they were pathologically diagnosed with stages I-III disease. The studies included patients who underwent laparotomy, da Vinci robot-assisted surgery, and minimally invasive laparoscopic surgery.

The exclusion criteria were missing blood test data, emergency surgery, stage IV disease, palliative surgery, and concurrent major surgery on other body parts or organs. Complete preoperative blood biochemistry and carcinoembryonic antigen (CEA) levels were recorded in patients undergoing elective colorectal surgery. On postoperative day three, a comprehensive follow-up blood and biochemical panel was reassessed.

The primary outcome of this study was defined as the occurrence of significant complications within a short-term period (30 days), indicated by a Clavien-Dindo score of ≥ 3. By analyzing patients with a Clavien-Dindo score of ≥ 3, this study aimed to identify blood test markers that could predict the occurrence of short-term postoperative complications and determine which of these markers provided the most accurate prediction rates.

We used a Clavien-Dindo score of ≥ 3 as a threshold to categorize patients into major and minor complication groups. The blood test values of these two groups were subjected to both univariate and multivariate analyses to identify significant blood markers. Subsequently, these significant blood markers were further analyzed using receiver operating characteristic (ROC) regression analysis to identify markers with predictive capabilities, aiming for those with an area under the curve (AUC) greater than 0.7.

Statistical analysis

The IBM SPSS 20 statistical package was used for data analysis. For continuous variables, the central tendency indicator was represented by the median. Continuous variables were assessed using Student's t-test for normally distributed data and the Mann-Whitney U test for data that did not follow a normal distribution. Categorical variables were compared using Pearson's chi-square test. Statistical significance was set at $p < 0.05$ (two-tailed).

To evaluate the predictive ability of blood and biochemical data in identifying postoperative complications, we categorized the complications into major complications (Clavien-Dindo score ≥ 3) and minor complications (Clavien-Dindo score < 3). ROC curve analysis was performed on the population with overall complications, followed by ROC curve analysis on the subgroup with Clavien-Dindo score ≥ 3.

This technique involves plotting the true positive rate (sensitivity) against the false positive rate (1-specificity). The effectiveness of the diagnostic tests was quantified by the area under the ROC curve (AUC).

Additionally, the ROC curve facilitated the determination of the optimal threshold values for various parameters, aiming to achieve the best combination of sensitivity and specificity for the most accurate diagnosis of the anticipated clinical outcomes.

The optimal cut-off points for blood values were determined using the slope of the ROC curve, defined as Slope = Sensitivity / (1 – Specificity). The optimal cut-off point is where the slope equals the ratio of the costs of false positives and false negatives, ensuring the best balance between sensitivity and specificity.

Results

A total of 1,298 patients underwent therapeutic surgical interventions between 2018 and 2020. After excluding 24 patients who underwent emergency surgeries, 425 with incomplete data, 106 with stage IV disease or who underwent palliative surgery, and 13 with benign tumors or concurrent surgeries, the study population comprised 730 individuals. Among these, 628 patients experienced no complications during hospitalization or within 30 days after surgery. The remaining patients encountered complications categorized using the Clavien-Dindo scoring system (Fig. 1).

The mean age of the participants was 63 years. There were no significant differences between the groups in terms of sex distribution, ASA scores, intraoperative blood loss, surgical duration, or comorbidities. Among all surgical procedures performed, low anterior resection (LAR) was the most commonly performed procedure, followed by right hemicolectomy and high anterior resection (HAR), accounting for 30.5% (n = 223), 27.1% (n = 198), and 26% (n = 190) of cases, respectively. Notably, the highest incidence of complications was observed in patients who underwent LAR (19.5%, $p = 0.001$), followed by those who underwent right hemicolectomy (12.1%), and then HAR (9.5%).

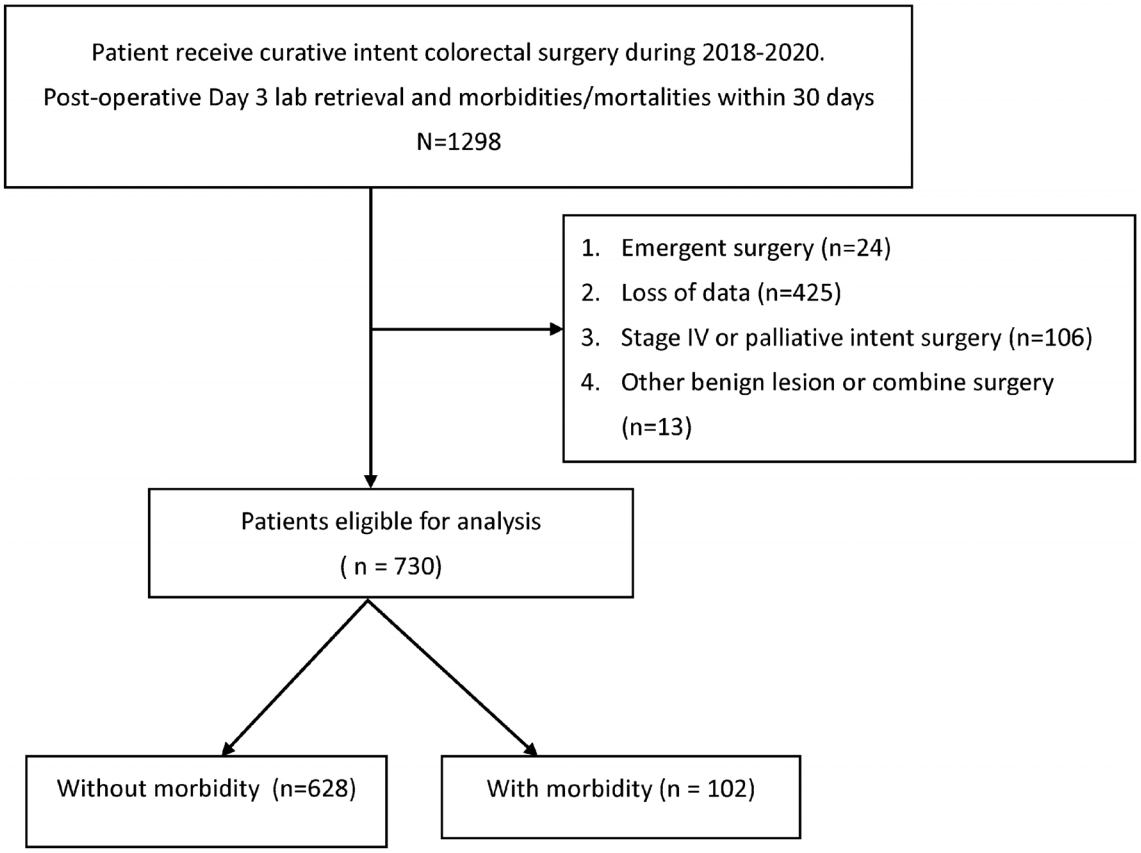


Fig. 1. Flow chart shows the study identification and inclusion processes.

Additionally, the study evaluated the incidence of complications among patients who underwent concurrent stoma creation during the same surgical procedure and revealed a relatively high complication rate of 33.3% (n = 4) in this group ($p = 0.016$) (Tables 1, 2).

Among the patients experiencing complications, the overall mortality rate was 2.9% (n = 3). All three patients who experienced mortality had undergone LAR. Two of these patients had multiple comorbidities. One had dialysis, diabetes, and hypertension, while the other had dialysis and a history of liver transplantation with long-term use of immunosuppressants. They developed leakage on postoperative days 7 and 12, respectively. Despite aggressive interventions, including temporary stool diversion and broad-spectrum antibiotic treatment, they experienced uncontrollable infections that led to mortality. The third patient experienced massive intraoperative bleeding due to tumor invasion into the presacral area. Postoperatively, this patient developed transfusion-related acute lung injury (TRALI) and acute respiratory distress syndrome (ARDS) in the ICU and died on postoperative day 30.

For the patients with Clavien-Dindo score ≥ 3 as a threshold, 16.7% (n = 17) experienced severe complications, such as anastomotic leakage, necessitating surgical reconstruction or stoma creation. The specific complications among the surgical methods were distributed as follows: right hemicolectomy (n = 198) had a morbidity rate of 12.1% (n = 24), including 1.5% (n = 3) for anastomotic leakage, 4.5% (n = 9) for

Table 1. Patient characteristics

Variables	Without morbidity (n = 628)	With morbidity (n = 102)	Total (n = 730)	*p* value
Age (mean ± SD)	63.24 ± 13.62	67.04 ± 14.71	63.77 ± 13.83	0.01
Male (%)	333 (53)	65 (63.7)	398 (54.5)	0.053
Comorbidities				
Diabetes mellitus (%)	168 (26.7)	28 (27.4)	196 (26.8)	0.086
Hypertension (%)	221 (35.1)	18 (17.6)	239 (32.7)	0.635
ESRD (%)	66 (10.5)	14 (13.7)	80 (11)	0.438
ASA (mean ± SD)	2.61 ± 0.49	2.71 ± 0.46	2.63 ± 0.49	0.081
Concurrent stoma creation	85 (78)	24 (22)	109 (14.9)	0.016
Operating time (min)	251.16 ± 136.47	258.38 ± 74.12	252.09 ± 129.51	0.646
Blood loss (ml)	67.30 ± 99.85	87.57 ± 84.83	70.82 ± 97.23	0.238

ESRD, end stage renal disease; ASA, American Society of Anesthesiology.

Table 2. Surgical methods and morbidities (mortality excluded)

	Total N (%)	With morbidities N (%)	Anastomotic leakage N (%)	Ileus N (%)	Pneumonia N (%)	UTI N (%)	SSI N (%)	Stress ulcer N (%)	Other complications N (%)	*p* value
Surgical methods										
Right hemicolectomy	198 (27.1)	24 (12.1)	3 (1.5)	9 (4.5)	2 (1.0)	3 (1.5)	4 (2.0)	2 (1.0)	1 (0.5)	0.239
Left hemicolectomy	64 (8.8)	3 (4.7)	1 (1.6)	0 (0)	0 (0)	1 (1.6)	1 (1.6)	0 (0)	0 (0)	0.086
High anterior resection	190 (26)	18 (9.5)	6 (3.2)	5 (2.6)	2 (1.1)	2 (1.1)	3 (1.6)	0 (0)	0 (0)	0.06
Low anterior resection	223 (30.5)	43 (19.5)	10 (4.5)	7 (3.2)	4 (1.8)	6 (2.7)	7 (3.1)	1 (0.4)	8 (3.6)	0.001
Transverse-colectomy	5 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NS
Subtotal colectomy	12 (1.6)	4 (33.3)	1 (8.3)	1 (8.3)	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (8.3)	NS
Abdominoperineal resection	13 (1.8)	1 (7.7)	0 (0)	1 (7.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NS
Hartmann's operation	11 (1.5)	4 (36.3)	0 (0)	1 (9.1)	0 (0)	0 (0)	2 (18.2)	0 (0)	1 (9.1)	NS
TaTME	14 (1.9)	2 (14.3)	1 (7.1)	0 (0)	0 (0)	1 (7.1)	0 (0)	0 (0)	0 (0)	0.052

UTI, urinary tract infection; TaTME, transanal total mesorectal excision; SSI, superficial surgical site infection.

ileus, 1.0% (n = 2) for pneumonia, 1.5% (n = 3) for urinary tract infection (UTI), 2.0% (n = 4) for superficial surgical site infection (SSI), 1.0% (n = 2) for stress ulcers, and 0.5% (n = 1) for other complications. Left hemicolectomy (n = 64) had a morbidity rate of 4.7% (n = 3), including 1.6% (n = 1) for anastomotic leakage, 1.6% (n = 1) for UTI, and 1.6% (n = 1) for SSI. High anterior resection (n = 190) had a morbidity rate of 9.5% (n = 18), including 3.2% (n = 6) for anastomotic leakage, 2.6% (n = 5) for ileus, 1.1% (n = 2) for pneumonia, 1.1% (n = 2) for UTI, and 1.6% (n = 3) for SSI. Low anterior resection (n = 220) had a morbidity rate of 19.5% (n = 43), including 4.5% (n = 10) for anastomotic leakage, 3.2% (n = 7) for ileus, 1.8% (n = 4) for pneumonia, 2.7% (n = 6) for UTI, 3.1% (n = 7) for SSI, 0.4% (n = 1) for stress ulcers, and 3.6% (n = 8) for other complications.

For other surgical methods, transverse-colectomy (n = 5) had no recorded morbidities. Subtotal colectomy (n = 12) had a morbidity rate of 33.3% (n = 4), including 8.3% (n = 1) for anastomotic leakage, 8.3% (n = 1) for ileus, 8.3% (n = 1) for SSI, and 8.3% (n = 1) for other complications. Abdominoperineal resection (n = 13) had a morbidity rate of 7.7% (n = 1), including 7.7% (n = 1) for ileus. Hartmann's operation (n = 11) had a morbidity rate of 36.4% (n = 4), including 9.1% (n = 1) for ileus, 9.1% (n = 1) for UTI, and 9.1% (n = 1) for other complications. Lastly, TaTME (n = 14) had a morbidity rate of 14.3% (n = 2), including 7.1% (n = 1) for anastomotic leakage and 7.1% (Tables 2, 3).

Univariate analysis of the blood test results revealed that patients with complications had higher levels of WBC ($p < 0.001$), segments ($p < 0.001$), lymphocytes ($p < 0.001$), alanine aminotransferase ($p = 0.039$) and CRP ($p < 0.001$). Further multivariate analysis identified lymphocytes ($p = 0.008$) and CRP levels ($p < 0.001$) on the third postoperative day as significant predictive markers (Table 4).

Regression analysis of these blood markers was performed. In the overall population, the AUC for CRP, segments, and WBC counts were 0.694, 0.663, and 0.612, respectively. The CRP cutoff value in this cohort was 68.66, with a sensitivity of 0.676 and a specificity of 0.643 (Fig. 2a).

Separate regression analysis of the blood test data from patients with severe complications (Clavien-Dindo ≥ 3) revealed an AUC of 0.721 for CRP and 0.684 for segments. The CRP cutoff value in this subgroup was 118.98, with a sensitivity of 0.567 and a specificity of 0.863 (Fig. 2b).

Discussion

Postoperative complications such as leakage and infections detrimentally affect a patient's quality of life, prolong hospital stay, and, in more severe cases, lead to increased mortality and morbidity.[8,9] In this study, the predictive capacity of CRP for severe complications proved to be superior compared to its predictive ability for the overall patient population. Notably, a CRP level of < 118 mg/dL on the third postoperative day was indicative of a lower risk of severe com-

Table 3. Postoperative complications stratified by Clavien-Dindo Score

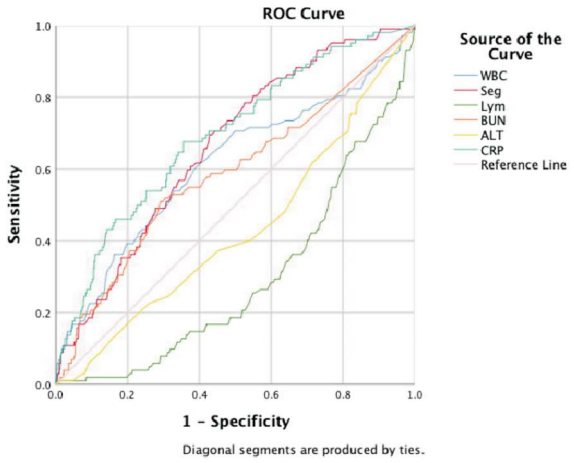
	N = 102 (%)
Major (Clavien-Dindo score ≥ 3)	
Anastomosis leakage, with surgical/percutaneous intervention	17 (16.7)
Revisit OR due to other complications (ureter injury, fascia dehiscence, ileus)	11 (10.8)
Mortality	3 (2.9)
Minor (Clavien-Dindo score < 3)	
Anastomosis leakage, with conservative treatment	8 (7.8)
Ileus	21 (20.6)
Pneumonia	8 (7.8)
Urinary tract infection	13 (12.7)
Superficial surgical site infection	18 (17.6)
Stress ulcer	3 (2.9)

Table 4. Blood test markers and univariate/multivariate analysis

	Preoperative	Postoperative Day 3	Univariate analysis	Multivariate analysis	
	Mean ± SD	Mean ± SD	*p* value	OR (95% CI)	*p* value
WBC (μL)	7201.16 ± 63.15	7420 ± 0.13	< 0.001	1.031 (0.964 ± 1.102)	0.375
Hemoglobin (g/dL)	12.26 ± 0.06	11.51 ± 0.06	0.936		
Seg (%)	63.01 ± 0.31	76.26 ± 0.24	< 0.001	0.979 (0.942 ± 1.019)	0.298
Lymphocytes (%)	26.8 ± 0.24	15.44 ± 0.29	< 0.001	0.924 (0.871 ± 0.980)	0.008
Band (%)		0.1 ± 0.01	0.065	1.059 (0.868 ± 1.292)	0.571
BUN (mg/dL)	16.02 ± 0.26	15.55 ± 0.59	0.27		
Creatinine (mg/dL)	0.91 ± 0.02	0.92 ± 0.03	0.592		
ALT (U/L)	25.4 ± 0.39	26.22 ± 0.56	0.039	0.971 (0.941 ± 1.002)	0.069
CRP (mg/L)	9.75 ± 0.6	68.67 ± 1.53	< 0.001	1.009 (1.004 ± 1.013)	< 0.001

WBC, white blood cell; Seg, neutrophil segmented; BUN, blood urea nitrogen; Band, neutrophil band; ALT, alanine aminotransferase; CRP, C-reactive protein.

(a) Overall population



(b) Patients with complications (Clavien–Dindo ≥ 3)

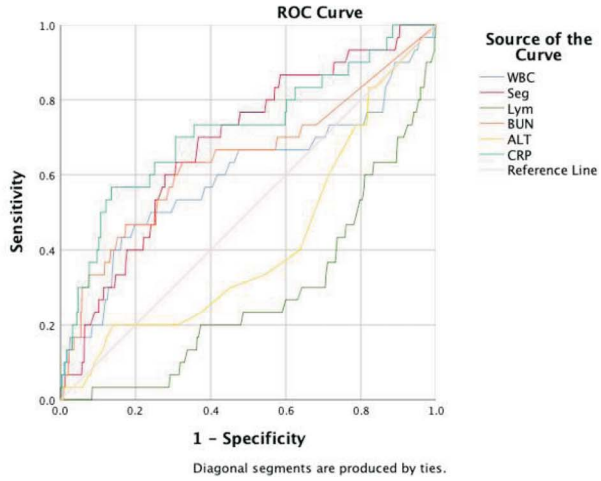


Fig. 2. ROC curve of blood test markers.

plications. Elevated postoperative CRP levels have been associated with an increased risk of complications such as infections, anastomotic leaks, and sepsis. According to ancillary studies, the predictive cutoff values for CRP on postoperative days three and four were < 124 mg/L and < 144 mg/L, respectively.[10] Research also demonstrated that CRP levels on postoperative days 3 to 5 are particularly useful in predicting complications. For example, a study found that CRP levels > 140 mg/L on postoperative day 3 were significantly associated with anastomotic leaks in colorectal surgery patients.[11]

Studies suggest that persistently high CRP levels beyond the initial postoperative days may indicate underlying issues that require intervention, also early detection and response can improve patient outcomes.[12]

CRP serves as a significant inflammatory marker, reflecting the body's response to surgical trauma and potential complications. The reasons for CRP elevation after colorectal surgery can be multifactorial. Surgical trauma itself induces an inflammatory response, resulting in increased CRP levels. Additionally, postoperative infections, anastomotic leaks, and other complications such as abscess formation or bowel obstruction contribute to elevated CRP levels. As a sensitive marker of inflammation, CRP is valuable for predicting postoperative complications and monitoring patient recovery.

Given its role, CRP can be used as a preventative measure by guiding clinical decisions. Enhanced mo-

nitoring of CRP levels postoperatively, especially on days 3 to 5, allows for early detection of complications. This enables timely interventions, such as additional diagnostic imaging or preemptive antibiotic therapy, potentially preventing severe outcomes. Utilizing CRP measurements can also inform decisions about patient discharge, ensuring those at higher risk of complications are identified and managed appropriately before leaving the hospital.

To improve the predictive ability of CRP across different patient populations, several strategies can be employed. First, dynamic monitoring of CRP levels, rather than relying on a single measurement, allows for early detection of complications. Second, combining CRP with other inflammatory markers, such as WBC, ESR, and PCT, can provide a more comprehensive prediction.

In the current medical landscape, where minimally invasive surgeries are increasingly prevalent, and most patients are discharged within a week after surgery, the ability to predict post-discharge complications during the in-hospital period is paramount. Utilizing CRP as a predictive biomarker can prevent the premature discharge of patients at risk of developing complications.[4] This approach aligns with findings from studies in other countries suggesting that a CRP level exceeding 172 mg/L may warrant extended hospital observation to mitigate the risk of adverse postoperative events.[13]

Compared with other studies, where the incidence of anastomotic leakage typically ranges between 3-10%,[14] the anastomotic leakage rate in this study was 3.4%. This relatively low rate may be predominantly attributed to the majority of surgeries being minimally invasive or to the proactive creation of stomas during surgery in high-risk patients. However, the presence of comorbid conditions in this patient subgroup indirectly contributed to the higher incidence of postoperative complications among those who underwent stoma creation.

The statistical analysis in Table 1a shows that older age is significantly associated with a higher incidence of postoperative complications. Elderly patients undergoing colorectal surgery are more prone to postoperative complications due to several factors. These include weakened immune function, multiple comorbidities (like hypertension and diabetes), reduced physical fitness and organ function, poor nutritional status, and lower surgical tolerance. Recognizing these risks is essential for improving their postoperative outcomes.

Consequently, CRP measurements on the third postoperative day could provide insights into whether a patient is eligible for early discharge. However, the feasibility of daily postoperative CRP tracking depends on the healthcare policies of each country and may not be uniformly implemented in all hospital settings.

A limitation of this study is rooted in the routine practice of conducting blood draws only on postoperative day three. This approach requires the use of additional diagnostic methods (such as imaging, physical examinations, or other non-invasive tests) beyond CRP measurements to effectively predict the occurrence of complications. However, another study involving 933 patients adopted a more comprehensive approach, performing preoperative and consecutive postoperative blood draws for five days, utilizing the trajectory of CRP levels as a predictive tool for complications. Their findings revealed that a daily postoperative increase in CRP levels exceeding 50 mg/L correlated with a high sensitivity of 0.85 for predicting anastomotic leakage and a negative predictive value of 0.99. Moreover, an increase in CRP levels by more than 50 mg/L from day 3 to day 4 or from day 4 to day 5 after surgery showed a high level of precision (specificity of 96-97%) in identifying patients who were likely to require intervention for leaks, as indicated by favorable positive likelihood ratios ranging from 4.99-6.44.[15] Nonetheless, under current healthcare systems, such an extensive regimen of blood draw tracking is not feasible, limiting the potential for achieving a higher AUC for CRP as a predictive marker.

This study deduced that a CRP level greater than 118 mg/L on the third postoperative day might indicate the potential for severe complications (Clavien-Dindo ≥ 3), with a sensitivity of 0.56 and a specificity of 0.86. Consequently, additional diagnostic procedures or interventions may be required in clinical practice to prevent potential complications. Although CRP

levels are commonly used to assess the degree of inflammation in patients undergoing abdominal surgery or those with infections, the predictive capability of this study was limited by a solitary blood draw conducted on the third postoperative day. It has been posited that a series of consecutive CRP measurements could enhance the predictive accuracy, thereby mitigating the risk of post-discharge complications or delays in treatment, enhancing patient outcomes, and the overall effectiveness of postoperative care.

Conclusion

This study deduced that a CRP level greater than 118 mg/L on the third postoperative day might indicate the potential for severe complications (Clavien-Dindo ≥ 3), with a sensitivity of 0.56 and a specificity of 0.86. Consequently, additional diagnostic procedures or interventions may be required in clinical practice to prevent potential complications.

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原　著

術後第三天的血液檢測對於接受手術患者的短期結果及併發症的預測能力

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目的　在接受常規大腸直腸癌手術病患中，吻合處滲漏是為一嚴重手術後併發症。以往，我們透過臨床表現及觀察引流管等方式來判斷病患是否發生嚴重併發症。這篇研究的目的在於透過比較術前及術後第三天的抽血指標，來預測病人是否會發生嚴重併發症。

方法　我們收錄了 2018-2020 年間接受常規大腸直腸手術病患共 1298 人。每位病人在手術前皆會接受完整的血液及生化學抽血檢查，接著術後第三天的血液、生化學檢查再與術前的抽血報告做多變項及迴歸分析。以找出最適合當作預測併發症的指標。

結果　在 1298 位病人中，最後納入統計的病人共 730 位。容易發生併發症的族群為高年紀及接受前位切除術患者。其中在多變項分析中具有統計上意義的預測指標為 Lymphocyte ($p = 0.008$) 及 CRP ($p < 0.001$)。迴歸統計則發現 CRP 對於 Clavien-Dindo Score ≥ 3 的 AUC 可達 0.72，其 cut off value 為 118.98 mg/L。

結論　術後第三天抽血的 CRP 值可當作預測病患是否會發生嚴重併發症的參考指標。讓我們在臨床上及早介入處理，以降低併發症造成的不良反應。

關鍵詞　術後併發症、術後第三天血液檢測、大腸直腸手術。